

**IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON**

IN RE ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	Master File No. 2:12-MD-02327 MDL 2327
THIS DOCUMENT RELATES TO: WAVE 4 CASES	JOSEPH R. GOODWIN U.S. DISTRICT JUDGE

**MEMORANDUM OF LAW IN SUPPORT OF MOTION TO EXCLUDE
THE OPINIONS AND TESTIMONY OF DR. VLADIMIR IAKOVLEV**

Ethicon, Inc.; Ethicon, LLC; and Johnson & Johnson (collectively, “Ethicon”), submit this memorandum in support of their motion to exclude the testimony of Dr. Vladimir Iakovlev. In *Nease v. Ford Motor Co.*, 848 F.3d 219 (4th Cir. 2017), the Fourth Circuit reaffirmed the importance of testing in determining the reliability of an expert’s opinion. Dr. Iakovlev’s failure to conduct tests to validate the hypothesis underlying his degradation opinions—coupled with scientific testing disproving his theory—demonstrates that his opinions cannot withstand *Daubert*. Ethicon requests a hearing pursuant to Federal Rules of Evidence 104(a) and 104(c) to demonstrate that Dr. Iakovlev’s testimony is inadmissible.¹

INTRODUCTION

Although the Court has permitted Dr. Iakovlev to testify on some issues in prior cases,² new case law, testing, and scientific literature prove that his methods are unreliable.

In *Nease*, the Fourth Circuit emphasized that testing, while not dispositive, is of critical importance in assessing whether an expert’s opinion is reliable. 848 F.3d at 231-32. Here, Dr.

¹ The cases to which this motion applies are identified in Ex.A.

² E.g., Mem. Op. and Order (*Daubert* Motion re: Vladimir Iakovlev, M.D., No. 2:12-md-02327 (S.D. W. Va. Sept. 1, 2016) [ECF # 2710] (“Wave 1 Iakovlev Order”).

Iakovlev has admitted: (a) that the central premise of his degradation opinions—that Prolene degrades *in vivo* causing it to trap stains in its degraded surface that are detectable using light microscopy—is a testable hypothesis; and (b) he has failed to test that hypothesis. *See* Ex. B, Iakovlev 3/21/16 *Stubblefield* Dep. 64:19-65:4.

Ethicon’s experts, on the other hand, have tested Dr. Iakovlev’s hypothesis and *disproven* his theory. Ethicon’s experts intentionally oxidized Prolene using two different approaches, applied the same sample preparation protocol and stains used by Dr. Iakovlev, and proved that oxidized Prolene does not hold stain.

Dr. Iakovlev’s opinions regarding the complications allegedly caused by Ethicon mesh products are similarly flawed. Dr. Iakovlev’s proposed biological mechanism—that degradation causes increased inflammation that, in turn, leads to pain—is also a testable hypothesis. But, again, Dr. Iakovlev never tested this hypothesis by comparing symptomatic and asymptomatic mesh explants. Other experts, however, have tested this theory, and proven that increased levels of inflammation in pelvic tissue are not correlated with increased pain. *See* Ex. C, A. Hill, *et al.*, *Histopathology of Excised Midurethral Sling Mesh*, 26 Int’l Urogynecology J. 591 (2015).

Similarly, Dr. Iakovlev’s opinion that every patient who experiences an erosion also suffers from an infection is pure speculation because he has made no effort to adhere to the standard criteria used by the medical community to determine whether an infection exists.

Dr. Iakovlev overreaches in basing his opinions on light microscopy and histological stains, as these tools do not permit even neuropathologists to make the sorts of conclusions regarding nerves and pain that Dr. Iakovlev offers. Additionally, Dr. Iakovlev’s opinions regarding mesh deformation and his novel “compartmentalization” theory are unsupported by scientific data or literature, and inconsistent with medical facts as to the female anatomy.

ARGUMENT

I. Legal Standard

Ethicon incorporates by reference the standard of review for *Daubert* motions as articulated by the Court in *Edwards v. Ethicon, Inc.*, No. 2:12-CV-09972, 2014 WL 3361923, at **1-3, (S.D. W. Va. July 8, 2014).

II. The Court Should Exclude Dr. Iakovlev's Degradation Opinions.

A. Dr. Iakovlev's degradation opinions are based on an untested hypothesis.

i. Testing is a key factor in determining the reliability of expert opinion.

In the recent case of *Nease v. Ford Motor Co.*, the Fourth Circuit reaffirmed the importance of testing to assess the reliability of an expert's opinion. The plaintiff in *Nease* crashed a truck he was driving because he was unable to stop, allegedly due to "mechanical binding" of the truck's speed-control cable. 848 F.3d at 221-23. The plaintiff's expert opined that the speed-control assembly in plaintiff's truck was defective because the design permitted contaminants to bind the speed-control cable, which resulted in the accident. *Id.* at 231.

The court explained that, while *Daubert* is a "flexible test" and no one factor is dispositive, "[o]ne especially important factor for guiding a court in its reliability determination is whether a given theory has been tested." *Id.* at 231. Without testing, an expert's theory may be plausible and "may even be right[,] . . . [but] it is no more than a hypothesis, and thus is not knowledge, nor is it based upon sufficient facts or data or the the product of reliable principles and methods applied reliably to the facts of the case." *Id.* (citation omitted).

In concluding that the expert's opinions were unreliable, the court focused on the fact that he failed to test his theory. Specifically, the court found that the expert "never tested [the truck] to determine whether it is actually possible for enough debris to accumulate" such that binding could occur, and "conceded that he never ran any tests to confirm his theory." *Id.* For this reason,

the court concluded that the expert's "failure to test his hypothesis renders his opinions on the cause of [the] accident unreliable." *Id.* In so holding, the court explained that while "scientific methodology involves generating hypotheses and testing them to see if they can be falsified," the expert merely "presented a hypothesis only [and] failed to validate it with testing." *Id.*³

Applying the teachings of *Nease* to Dr. Iakovlev's "bark" theory, it is clear that the Court should exclude his opinions as unreliable for the same reasons.

ii. Absent Dr. Iakovlev's purported observation of degradation "bark" through his microscope, all of his degradation opinions exceed his qualifications.

Dr. Iakovlev's degradation opinions are based on a testable hypothesis that he admits he has failed to test. Specifically, Dr. Iakovlev asserts that Prolene degrades *in vivo*, creating cracks that trap histological stains, which he detects as a "bark" layer around the fiber via light microscopy. *See* Ex. D, Expert Report of Dr. Vladimir Iakovlev ("Iakovlev Report"), at 8-9, 18-19 (discussing degradation theories). All of the other pathology opinions Dr. Iakovlev seeks to offer about the existence of degradation depend on this purported observation.

Previously, the Court did not credit Ethicon's argument on the grounds that "Dr. Iakovlev's testimony on degradation generally is extensively supported with specific references to the scientific literature and several internal documents." Mem. Op. and Order (*Daubert* Motion re: Vladimir Iakovlev), at 6 (S.D. W. Va. Sept. 1, 2016) [ECF # 2710]. But Ethicon respectfully submits that, without his bark theory, Dr. Iakovlev's opinion that Prolene degrades *in vivo* constitutes a materials science opinion that he is not qualified to offer. *See* Ex. E, *Bellew* 3/5/15 Trial Tr. 696:13-20 (admitting that he is not a materials scientist, and has not consulted with one); Ex. F, Iakovlev 3/18/14 *Huskey* Dep. 211:15-17 (did not consult a materials scientist).

³ The court found that the remaining *Daubert* factors likewise supported exclusion of the expert's opinion because (i) he failed to publish or otherwise subject his theory to peer review; (ii) his poor "methodology" rendered it impossible to determine a potential rate of error; and (iii) a company document identifying potential failure modes did not constitute "general acceptance" of the expert's theory. *Id.* at 232-33.

Dr. Iakovlev's alleged detection of histological stain trapped in the degraded surface of Prolene is the only aspect of his degradation opinions related to his knowledge, skill, experience, training, or education as a pathologist. Absent these purported observations, Dr. Iakovlev offers opinions about the condition of the surface of a polymer simply by pointing to studies and internal Ethicon documents that bear no relationship whatsoever to pathology.

iii. Dr. Iakovlev's reliance on an untested hypothesis is inconsistent with the scientific method.

As the Fourth Circuit recognized, proper "scientific methodology involves generating hypotheses and testing them to see if they can be falsified." *Nease*, 848 F.3d at 232. Although Dr. Iakovlev's "bark" theory is the lynchpin of his degradation opinions, he failed to test whether it is even possible for degraded Prolene to trap stain. Like the expert in *Nease*, Dr. Iakovlev has "presented a hypothesis only—he failed to validate it with testing." *See id.*

Dr. Iakovlev concedes that his theory is capable of being tested by intentionally oxidizing pristine Prolene to determine (i) whether it degrades and, if so, (ii) whether it holds stain. *See Ex. G, Iakovlev 9/11/15 Dep. 31:14-46:13* (discussing testing to determine whether oxidized Prolene traps stain). In fact, Dr. Iakovlev testified in September 2015 that he was conducting such a test to validate his hypothesis. *Id.*⁴ In March 2016, Dr. Iakovlev admitted that he had not conducted this test. *See Ex. B, Iakovlev 3/21/16 Stubblefield Dep. 64:19-65:4*. It has been over 3 years since Dr. Iakovlev first offered his bark theory, and over 1½ years since he claimed he was testing it, but he still has not disclosed any such testing.

⁴ Notably, even in this incomplete test, Dr. Iakovlev failed to follow the scientific method. He did not prepare or follow a testing protocol, *Ex. G, Iakovlev 9/11/15 Dep. 32:24-33:6*; has no lab documentation, *id.* at 35:2-13; could not identify the meshes being tested, *id.* at 34:21-35:1, or even the number of samples, *id.* at 32:9-12; and could not identify the composition of the oxidative medium, *id.* at 34:5-14. Further, he frequently contradicts himself as to the amount of time necessary for degradation to occur. *Compare Ex. H, Iakovlev 4/19/2016 Ramirez Dep. at 394:15-21* (degradation appears at 1 year) with *Ex. I, Iakovlev 3/4/2016 Vignos-Ware Dep. at 39:11-24* (degradation observed at 8 months). As this Court has recognized, "[v]igorous adherence to protocols and controls are the hallmarks of 'good science.'" *Sanchez v. Bos. Sci. Corp.*, No. 2:12-cv-05762, 2014 WL 4851989 (S.D. W. Va. Oct. 17, 2014).

Thus, the foundational premise upon which all of Dr. Iakovlev's degradation opinions rest is merely a hypothesis. As Judge Posner explained, "the courtroom is not the place for scientific guesswork, even of the inspired sort. Law lags science; it does not lead it." *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 319 (7th Cir. 1996). The Court should preclude Dr. Iakovlev from offering his untested bark theory at trial on this basis alone. *See Nease*, 848 F.3d at 232.

iv. Ethicon's experts have disproven Dr. Iakovlev's hypothesis.

In *Nease*, the Fourth Circuit emphasized that, not only had the plaintiff's expert failed to validate his theory with testing, but the defendant's expert (Dr. Steven MacLean) had disproven a central component of the plaintiff's expert's hypothesis through testing. 848 F.3d at 225. Indeed, the court observed that the plaintiff's expert "never tested [the truck] to determine whether it is actually possible" for his theory to occur. *Id.* at 232. Instead, he "simply relied upon his [visual] observations" of the speed control cable via a fiber-optic tool commonly used by vehicle engineers. *Id.* at 226. Remarkably similar circumstances obtain in this litigation.

To determine the validity of Dr. Iakovlev's theory, Ethicon retained the same expert the Fourth Circuit relied on in *Nease*—Dr. Steven MacLean—who used appropriate scientific methods to test Dr. Iakovlev's hypothesis. *See* Ex. J, Expert Report of Dr. Steven MacLean ("MacLean Report"). To do so, Dr. MacLean intentionally oxidized Prolene mesh samples, then applied the same stains used by Dr. Iakovlev to the samples to determine whether the Prolene retained the stain. *See id.* at 78-96. Specifically, Dr. MacLean intentionally oxidized Prolene mesh samples using two different methods: (i) exposure to UV radiation, and (ii) exposure to the oxidative medium used by Drs. Guelcher and Dunn—experts for plaintiffs in pelvic mesh litigation. *Id.* at 78-81. Dr. MacLean's analysis using both approaches proved that even intentionally oxidized Prolene does not trap histological stain. *Id.* at 82-86.

In stark contrast, Dr. Iakovlev did not conduct any tests to validate his bark theory. Rather, like the expert in *Nease*, Dr. Iakovlev simply relied on his observations of bark to support his degradation opinions. *See* 848 F.3d at 226. And like the expert in *Nease*, Dr. Iakovlev's unreliable opinions should be excluded.

Additionally, Exponent's investigation proved that the bark-like outer layer surrounding Prolene fibers in Dr. Iakovlev's images is the result of various imaging artifacts. Ex. J, MacLean Report at 89-96. Among other things, Exponent's analysis demonstrated the following:

- Shading and other artifacts can be produced by manipulating a microscope's polarizers when viewing the fibers. *See id.* at 91-93 (microscopy slides are prepared using a microtome to cut the mesh fibers, which causes variations in the thickness of the fibers in the slide which "can create edge artifacts under polarized light").
- The appearance of a purple hue in some of Dr. Iakovlev's images is the product of exposing the specimen to plane-polarized light. *See id.* at 94.
- Differences in the material density between a sample and its surroundings can cause the appearance of lines that seem to separate the two substances, and which can be altered by changing the focus of the microscope. *See id.* at 93-94.
- The sample preparation process can result in differences in fiber thickness in individual fiber samples which, in turn, can cause stains to collect in pockets between the fiber and glass slide. *See id.* at 89-91. When viewed through a microscope, these pockets of stain create the illusion that the fiber sample is stained. *See id.* at 91.

Thus, Exponent—using a valid, documented, and repeatable scientific methodology—has established that Dr. Iakovlev's methods are flawed.

This is not a case of mere disagreement between the results offered by the parties' experts. Dr. Iakovlev has not presented *results*; he has offered only *hypothesis* that is untested and unsupported by scientific literature (as discussed below). *See Nease*, 848 F.3d at 232; *Claar v. Burlington N. R.R.*, 29 F.3d 499, 502-03 (9th Cir. 1994) ("Coming to a firm conclusion first and then doing research to support it is the antithesis of [the scientific] method."). Conversely, Dr. MacLean applied the scientific method to Dr. Iakovlev's hypothesis, and proved that his

degradation opinion is the product of flawed methodology.⁵ For all of these reasons, the Court should preclude Dr. Iakovlev from testifying based on this disproven theory.

B. Dr. Iakovlev's degradation theory is not supported by scientific literature.

Dr. Iakovlev has testified and written that he is the first person to propose the theory that degraded Prolene traps stain observable using light microscopy. *See* Ex. M, V. Iakovlev, *et al.*, *Pathology of Explanted Transvaginal Meshes*, 8 Int'l J. Med., Health, Pharm. and Biomed. Eng'g 512 (2014) ("The degradation bark is easily visible by routine microscopy, yet escaped pathologists for over 50 years."); *see also* Ex. N, Iakovlev 12/17/14 *In re Bos*. Sci. Dep. 194:4-6 ("I'm the first one who is describing light microscopy features of polypropylene degradation."). Dr. Iakovlev admits that his theory is not based in prior studies. *See* Ex. G, Iakovlev 9/11/15 Dep. 36:10-16 (explaining that he did not consult anyone because "[n]obody did it before").

Notably, Dr. Iakovlev admits that there is no published literature describing degradation bark in polypropylene other than his own. *See* Ex. O, Iakovlev, *Degradation of Polypropylene In Vivo*, at 7 ("[W]e found no description of these findings in published literature after a search through online and printed sources."); Ex. F, Iakovlev 3/18/14 *Huskey* Dep. 275:8-13. Indeed, a review paper Dr. Iakovlev co-authored recognizes that "the question of whether polypropylene degrades *in vivo* has not been fully resolved, despite decades of use." Ex. P, Blaivas, *et al.*, *Safety Considerations for Synthetic Sling Surgery*, *Nature Reviews Urology* at 17 (2015).

Given the dearth of literature supporting his theory, and the fact that his own writings question the existence of *in vivo* degradation, it cannot be said that Dr. Iakovlev's theory has garnered general acceptance by the scientific community. *See* Ex. N, Iakovlev 12/17/14 *In re*

⁵ Notably, Dr. MacLean's work based on this testing was accepted without revision for publication and presentation in a peer-reviewed conference proceeding by the Society of Plastics Engineers. Ex. K, MacLean 4/18/2016 Dep. at 129:22-131:18; *see also* Ex. L, S. Benight, *Microscopy of Intentionally Oxidized Polypropylene-Based Mesh Material*, SPE ANTEC (2016). The study reports on his testing conducted in connection with *Mullins v. Ethicon*. Ex. K, MacLean 4/18/2016 Dep. at 130:12-17.

Bos. Sci. Dep. 239:15-240:2 (admitting that he wrote the only published paper reporting that degraded polypropylene traps stain); Ex. Q, Expert Report of Juan C. Felix (“Felix Report”) 27 (“[T]he methodology of identifying degraded polypropylene using stains used for biologic tissue is not accepted by the majority of experts” because histology “[s]tains such as H&E work by attaching to structures with different ionic charges,” and “are not trapped like a cup would hold water”). Accordingly, the Court should preclude Dr. Iakovlev from testifying in this case.

This is exactly what *Daubert*’s gatekeeping function is designed to address. Given the complexity of these issues, there is no way to know if vigorous cross-examination is sufficient to cure Dr. Iakovlev’s scientifically flawed opinions. *See Nease*, 848 F.3d at 231 (“For the district court to conclude that [] reliability arguments simply go to the weight the jury should afford [the expert’s] testimony is to delegate the court’s gatekeeping function to the jury.”).

Because of the methodological flaws inherent in Dr. Iakovlev’s opinions, they should not be considered by the jury due to the significant risk of confusion and misunderstanding these technical scientific principles. *In re Digitek*, 821 F. Supp. 2d 822, 839 (S.D. W. Va. 2011) (expert opinion is inadmissible as “inconsistent with good science” if he makes “overreaching or speculative conclusions . . . based upon overreaching or speculative methodologies”).

C. Dr. Iakovlev’s opinion that degradation causes clinical complications is unreliable.

Dr. Iakovlev plans to tell the jury that it is proven that degradation of Prolene implanted in women causes various complications. Ex. D, Iakovlev Report at 8-9. But Dr. Iakovlev fails to identify any testing or scientific literature that supports the proposition that the degradation of Prolene in Ethicon mesh products causes any clinical complication. *See id.* at 8-10, 18-19. Dr. Iakovlev should be precluded from offering any such opinions on this basis alone. *See Nease*, 848 F.3d at 234 (explaining that opinion “unsupported by any evidence such as test data or relevant literature in the field” should be excluded).

Moreover, although the Court disagreed with its arguments in its Wave 1 Iakovlev Order, Ethicon respectfully submits that Dr. Iakovlev's publications do not provide a sufficient foundation for him to opine to a reasonable degree of medical certainty that degradation actually causes complications in patients. Indeed, Dr. Iakovlev's publications state only that degradation "*may play a role*" in the development of complications, and that studies are necessary to determine if degradation plays a role in causing complications.⁶

Simply put: a paper that states "A *may* cause B," is hardly a legitimate scientific basis for concluding that "A *does* cause B."

The Court should not permit Dr. Iakovlev to testify that degradation of Prolene causes complications when he failed to identify any support for his opinion, and his publications show that no such causal connection has been made, and even cast doubt on whether degradation occurs *in vivo*. See *Kumho*, 526 U.S. at 152 (experts must "employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.").

III. Dr. Iakovlev's Opinions Regarding Complications Are Unreliable.

A. Dr. Iakovlev's analysis is unreliable because he failed to use a control.

Dr. Iakovlev's opinions that Ethicon mesh products cause complications in women are based on his histological analysis of explanted meshes. Dr. Iakovlev's opinions are inconsistent with the scientific method because he failed to compare his histological observations to an

⁶ Ex. R, V. Iakovlev, *In Vivo Degradation of Surgical Polypropylene Meshes: A Finding Overlooked For Decades*, 465 *Virchows* (2014), at 35 ("discovery" of degradation using stains and microscopy "opens the door to study the role of degradation in the development of complications."); Ex. S, V. Iakovlev, *Explanted Surgical Meshes: What Pathologists and Industry Failed to Do for 50 Years*, 465 *Virchows* 337 (2014) ("The newly described findings need to be studied in correlation with clinical symptoms to guide future developments."); Ex. M, V. Iakovlev, *Pathology of Explanted Transvaginal Meshes* 512 (2014) ("Polypropylene degradation *may play a role* in the continuous inflammatory response, mesh hardening, and late deformations" and the "chemical products of degradation *need to be studied* for their composition and effect on the tissue."); Ex. O, Iakovlev, *Degradation of Polypropylene In Vivo* at 10 ("[The] exact mechanisms of these late complications are yet to be understood"); Ex. P, Blaivas, at 17 ("the question of whether polypropylene degrades *in vivo* has not been fully resolved, despite decades of use.").

asymptomatic comparator. *See* Ex. Q, Felix Report at 11-12; Ex. T, Expert Report of Teri Longacre at 5; Ex. U, Expert Report of Roger McLendon (“McLendon Report”) at ¶ 6; Ex. V, Expert Report of Hannes Vogel (“Vogel Report”) at 14. Dr. Iakovlev’s failure to use a control means that he cannot eliminate the likelihood that the histological presentation of women suffering from pain is the same as the histology of women not suffering from pain. *See* Ex. Q, Felix Report at 12; Ex. V, Vogel Report at 14.

This is a significant flaw in Dr. Iakovlev’s analysis because if the histology of both groups is the same, the histological findings do not identify the cause of the pain. *See* Ex. Q, Felix Report at 12. The same holds true with respect to all of the complications to which Dr. Iakovlev opines. Without a control, Dr. Iakovlev’s attempted correlation of specific complications to histological features is nothing but conjecture. *See Sanchez v. Bos. Sci. Corp.*, No. 2:12-cv-05762, 2014 WL 4851989 (S.D. W. Va. Oct. 17, 2014) (“Vigorous adherence to protocols and controls are the hallmarks of ‘good science.’”).

For this reason, the Court excluded Dr. Iakovlev’s opinions regarding complications in its September 1, 2016 Order. *See* Wave 1 Iakovlev Order at 8-9. The same result should obtain here.

B. Dr. Iakovlev failed to account for relevant scientific literature.

Dr. Iakovlev’s opinions are unreliable because he failed to account for scientific literature relevant to his opinions.⁷ As various courts have recognized, “if the relevant scientific literature contains evidence tending to refute the expert’s theory and the expert does not acknowledge or account for that evidence, the expert’s opinion is unreliable.” *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp. 2d 398, 425 (S.D.N.Y. 2005); *see also id.* at 425 n. 164 (noting courts have excluded expert testimony for failing to account for contrary evidence); *Yates v. Ford Motor Co.*,

⁷ The Court disagreed with Ethicon’s argument on the grounds that “Dr. Iakovlev’s alleged failure to review a particular study in forming his opinion is better suited for cross examination[.]” *Id.* at 9. Ethicon respectfully submits, however, that Dr. Iakovlev failed to account for numerous studies directly relevant to his opinions.

113 F. Supp. 3d 841, 858-59 (E.D.N.C. 2015) (same regarding scientific literature); *In re Zolof Prods. Liab. Litig.*, 26 F. Supp. 3d 449, 459-60 (E.D. Pa. 2014) (excluding expert who failed to distinguish studies directly relevant to her opinions).

Most significantly, Dr. Iakovlev did not address Dr. Hill's *Histopathology of Excised Midurethral Sling Mesh*, 26 Int'l Urogynecology J. 591 (2015) in his Report or publications. Indeed, Dr. Iakovlev was unaware of the Hill study until counsel for Ethicon identified it for him at deposition in the *Mullins* case. *See* Ex. G, Iakovlev 9/11/15 Dep. 152:14-153:8 (testifying that the only studies he found in a literature search for studies comparing histology for meshes removed for pain against meshes removed for non-pain reasons addressed hernia repair).

The Hill study conducted the analysis that Dr. Iakovlev has never done—*i.e.*, using a control and comparing the histological reaction of symptomatic and asymptomatic meshes. The authors examined 130 explanted meshes, and conducted a histological comparison of the patients who complained of pain and those who did not. Ex. C, Hill at 592. Contrary to their own hypothesis, they found that pain was *not* associated with increased inflammation. *Id.* at 592-93. They also found no difference in fibrosis between the two groups. *Id.* at 593.

Dr. Iakovlev's failure to account for literature directly relevant to his opinions is not an isolated incident,⁸ rendering his opinions unreliable. *In re Rezulini*, 369 F. Supp. 2d at 425.

C. Dr. Iakovlev's own paper proves his methodology is not scientifically legitimate.

It cannot be said that an expert's in-court opinion that contradicts his own out-of-court writings is reliable. Outside of the context of litigation, Dr. Iakovlev admits his approach is

⁸ *See, e.g.*, Ex. U, McLendon Report at ¶ 8 (Dr. Iakovlev's "[s]tatements relating pain pathogenesis to fibrous tissue about the mesh fail to explain why published studies reporting microscopic findings of post-operative meshes reveal a normal number and density of nerve fibers in the tissue."); *id.* at ¶ 10 (Dr. Iakovlev's opinion that mesh-related inflammation causes pain ignores study finding fewer inflammatory cells and fibroblasts, as well as unchanged numbers of granulocytes, lymphocytes, and monocytes in pre-op transvaginal biopsies than post-op); Ex. Q, Felix Report at 16 (Dr. Iakovlev's opinion that scar tissue associated with mesh contracts, leading to compression of tissues and organs is "clinically unfounded based on [a] compilation of clinical studies in meta-analyses").

inadequate. *See* Ex. P, Blaivas, at 15 (“[s]everal studies have confirmed” that “when microscopy [is] performed, results of the microscopic examinations usually d[o] not explain the specific complications experienced by the patients.”). His paper explains that “human tissue interactions with the mesh are known, but we have an incomplete understanding of interactions specific to a mesh material and design as well as the pathophysiology of any complications.” *Id.*

Although this Court disagreed with the significance of Dr. Iakovlev’s concession, Ethicon respectfully submits that an expert should not be permitted to opine about complications based on microscopy when his own writings explain that such analysis “d[oes] not explain the specific complications experienced by the patients.” *Id.* at 15; *see also Kumho*, 526 U.S. at 152 (explaining that an expert must “employ[] in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.”).⁹

D. Dr. Iakovlev’s opinions are speculative.

Although his own paper stated that the review of histology is insufficient for correlating complications to mesh, Dr. Iakovlev seeks to do just that. At deposition, however, Dr. Iakovlev has admitted that he could not draw causal conclusions based on his review of histological slides; instead, he “can only estimate the probability.” Ex. G, Iakovlev 9/11/15 Dep. 140:14-141:8; *see also id.* at 159:2-160:4 (acknowledging that he could not rule out that “deformed” nerve did not cause pain because “there are many, many, many factors which cause” symptoms); *id.* at 208:25-209:22 (admitting that he cannot opine that mesh caused symptoms in a specific slide because “[c]linical symptoms is [sic] a multifactorial, complex phenomena” but “probability that it will compress urethra is higher”); *id.* at 224:9-225:3 (claiming mesh fibers “[p]robably” irritated the

⁹ As further evidence of the lack of reliability of Dr. Iakovlev’s opinions, he has admitted at deposition that he alters the images used in his expert reports using Photoshop software. *See* Ex. W, Iakovlev 11/5/15 *Carlino* Dep. 110:1-117:9. Specifically, he changes the images to reflect what he believes to be consistent with what he sees in the microscope. *Id.* at 111:15-112:8.

nerve in the slide, but refusing to say the mesh “actually caused symptoms”). Dr. Iakovlev’s speculative conclusions are inconsistent with the scientific method, and should be excluded. *See In re Digitek*, 821 F. Supp. at 839.

E. Dr. Iakovlev lacks specialized knowledge sufficient to testify regarding potential injuries to the female body.

Dr. Iakovlev seeks to offer various opinions in this case as to how alleged defects in Ethicon mesh products cause complications in patients. But Ethicon’s gynecological pathologist and neuropathologists explain that Dr. Iakovlev’s opinions are predicated on fundamental errors of anatomy and physiology, as well as the manner in which nerves sense and transmit pain.

For example, Dr. Iakovlev’s opinion that thromboses and occlusions of capillaries and arterioles are evidence of complications related to Ethicon mesh products, *see* Ex. D, Iakovlev Report at 17, 62-64, show that he is unaware that such features are “commonplace throughout the body and have never been shown to be associated with pain,” *see* Ex. Q, Felix Report at 23.

Despite Dr. Iakovlev’s claims that connection of Ethicon mesh products “to the smooth muscle of the vaginal wall can interfere with its contraction (intercourse etc.),” Ex. D, Iakovlev Report at 17, striated muscles in the pelvis are responsible for contraction of the vagina during intercourse and these muscles are not affected by an implant, *see* Ex. Q, Felix Report at 13.

Dr. Iakovlev also testified that the presence of smooth muscle in mesh pores reveals that the mesh has migrated because smooth muscle has a restricted ability to regenerate. Ex. G, Iakovlev 9/11/15 Dep. 190:1-191:1. Dr. Iakovlev’s statement is simply false. Ex. Q, Felix Report at 13-14 (explaining the “generally accepted fact” that “[s]mooth muscle is able to regenerate in response to injury, such as surgery”).

Although Ethicon is aware that the Court disagreed with its arguments, Ethicon respectfully notes that these are not theories subject to interpretation, but facts generally accepted

by the medical community. Dr. Iakovlev should not be permitted to opine that Ethicon mesh products cause complications on areas of the body about which he has no specialized knowledge. *See Hines v. Wyeth*, No. 2:04-cv-0690, 2011 WL 2680842, at *7 (S.D. W. Va. July 8, 2011) (expert opinion must not go “beyond the expert[‘]s qualifications”).

IV. Dr. Iakovlev’s Opinions Regarding Pain Are Inconsistent With The Scientific Method and Medical Facts.

Dr. Iakovlev is not a neuropathologist. Yet, he offers numerous opinions premised on the erroneous assumption that the presence of nerve twigs (microscopic branches of nerves) on histological slides are indicative of pain. He opines that the growth of nerves through and around mesh causes pain by direct mechanical irritation. *See* Ex. D, Iakovlev Report at 11-12; 15-16. Similarly, he asserts that innervation of scar tissue around Ethicon mesh products causes pain by “direct mechanical irritation of the nerves as well as irritation of the receptors by inflammatory and physical mechanisms of pain.” *Id.* at 15. He also claims that the chronic inflammatory response caused by Ethicon mesh products results in increased pain sensitivity. *Id.* at 16.

Dr. Iakovlev bases these opinions on his analysis of slides depicting nerve twigs adjacent to mesh and present in scar tissue. *See id.* at 24-30 (slides showing mesh and scar tissue); *id.* at 31-38 (slides showing innervation of mesh in the “scar plate”); *id.* at 44 (slides showing innervation of mucosa overlying mesh).

As Drs. Hannes Vogel and Roger McLendon—Ethicon’s neuropathologists in this litigation—explain, Dr. Iakovlev’s conclusion that the mere observation of a nerve twig in scar tissue or the proximity of a nerve to mesh are sufficient to conclude that the patient suffered from pain reveal both a flawed methodology and a misunderstanding of the structure and function of nerves. Nerves in the human body are specialized, and only sensory nerve fibers are capable of transmitting pain signals. *See* Ex. U, McLendon Report at 9 (explaining function of motor,

autonomic, and sensory nerves); Ex. V, Vogel Report at 3-6 (same). Thus, one cannot link a specific nerve to pain without first determining that it is, in fact, a sensory nerve.

Even if it is a sensory nerve fiber, one must identify a sensory receptor to ascertain the type of signal the nerve carries. *Id.* at 6; *see also id.* at 4 (sensory nerves carry different signals); Ex. U, McLendon Report at 9 (same). One cannot draw a conclusion regarding pain without identifying a sensory receptor, because sensory receptors—not the nerve fiber—trigger the transmission of pain signals. Ex. U, McLendon Report at 9 & ¶ 14; Ex. Q, Felix Report at 22.

Dr. Iakovlev's reliance on light microscopy and stains does not permit him to make causal conclusions regarding pain. Dr. Iakovlev bases his pain opinions on his review of histological slides at low power, and the use of S100 and neurofilament to identify nerves. Yet, as Dr. Vogel explained, even neuropathologists cannot differentiate between nerve types via light microscopy. *See* Ex. V, Vogel Report at 6. And while stains like S100 and neurofilament help identify nerve parts, "specifically Schwann cells and axons, respectively," they cannot distinguish between nerve types and "do not identify sensory receptors." *Id.*

Dr. Iakovlev's lack of familiarity with the pathophysiology of nerves not only demonstrates a lack of specialized knowledge regarding the issues about which he seeks to testify, it contributed to his failure to apply a scientifically legitimate methodology for concluding that Ethicon mesh products cause pain in women.

Dr. Iakovlev's pain opinions are illustrative of the lack of a legitimate methodology underlying his opinions, but the inadequacies of his attempt to base causal conclusions on his histology apply with equal force to all of his opinions regarding the alleged complications caused by Ethicon mesh products. *See id.* at 7 (Dr. Iakovlev's "attribution of clinical symptoms to his histology is completely without reliable basis in the science of pathology.").

V. Dr. Iakovlev’s Opinion that the Presence of an Erosion Necessarily Implies that the Patient had a Wound Infection is Unreliable.

Dr. Iakovlev opines that Ethicon mesh products cause erosions in patients, and an erosion necessarily proves that the patient has an infection. Specifically, Dr. Iakovlev testified that “erosion is always associated with localized infection.” Ex. X, Iakovlev 3/13/16 *McBrayer* Dep. 14:2-6; Ex. Y, Iakovlev 3/4/16 *Funderburke* Dep. 25:12 (same); *see also id.* at 24:17-25:21 (“[A] diagnosis was made [of] vaginal erosion, which comes together with infection”). Dr. Iakovlev offers this opinion even in cases where he did not examine an explant. *See* Ex. X, Iakovlev 3/13/16 *McBrayer* Dep. 13:16-22. Dr. Iakovlev’s infection opinion is simply false.

It is well-understood in the medical community that certain criteria must be satisfied before an infection can be diagnosed. *See, e.g.*, Ex. Z, Guideline for Prevention of Surgical Site Infection, at 252 (1999) (“SSI Guidelines”); *see also* Ex. AA, Expert Report of Daniel Sexton at 8-11. Indeed, the Centers for Disease Control and Prevention (“CDC”) publishes criteria for determining whether an infection exists in various circumstances. For example, to diagnose a soft-tissue infection, a patient must have (i) “organisms identified from tissue or drainage from affected site by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment”; (ii) “purulent drainage at affected site”; or (iii) an abscess or other evidence of infection on gross anatomic or histopathological exam.” Ex. BB, *CDC/NHSN Surveillance Definitions for Specific Types of Infections*, at 17-25 (Jan. 2016).¹⁰

In this litigation, Dr. Iakovlev made no effort to adhere to diagnostic criteria in forming his infection opinions. Contrary to the generally accepted practice of the medical community, Dr.

¹⁰ To diagnose a post-operative surgical site infection, an infection must involve at least one of the following: Purulent drainage from the deep incision . . . [;] A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative[;] An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiologic examination[; or,] Diagnosis of a deep incisional SSI by a surgeon or attending physician. Ex. Z, SSI Guidelines; *see also* Ex. CC, Global Guidelines for the Prevention of Surgical Site Infection, at 38 (2017) (identifying various infection criteria).

Iakovlev believes that no such analysis is necessary, because “it’s a given that there is infection” any time there is an erosion. *See, e.g.*, Ex. Y, Iakovlev 3/4/16 *Funderburke* Dep. 24:17-25:21. Moreover, Dr. Iakovlev explained that he ignores medical records in his infection analysis based on his unsubstantiated belief that an infection will invariably accompany an erosion. *Id.* at 25:22-26:7 (“Maybe [a medical record regarding infection] is there but I wouldn’t pay attention[.]”).

Finally, Dr. Iakovlev’s opinion ignores the fact that erosions are generally treated—and resolve—with topical estrogen cream without the use of antibiotics. In other words, Dr. Iakovlev’s infection opinion simply makes no sense because the medical community’s standard method to treat erosions does not involve a course of action designed to treat an infection.

VI. Dr. Iakovlev’s Opinions Regarding Mesh Folding/Deformation Are Unreliable.

Dr. Iakovlev opines that mesh can fold or curl *in vivo*, and that such deformations can form “compartments.” Ex. D, Iakovlev Report at 11, 17. He claims that mesh folding, curling, and compartments can cause pain. *Id.* at 11. But Dr. Iakovlev fails to identify any support for this novel theory. *See* Ex. V, Vogel Report at 14 (explaining that this theory is “unprecedented in the surgical or pathology medical literature regarding synthetic sling surgery”).

Dr. Iakovlev’s claim that he can look at a pathology slide and infer that mesh curled or deformed *in vivo* prior to explantation is unfounded. Dr. Iakovlev failed to follow the standard methodology used by pathologists for determining how a specimen is oriented in the human body. *See* Ex. DD, William Westra, *Surgical Pathology Dissection* (2003), at 4; Ex. EE, Susan Lester, *Manual of Surgical Pathology* (2010) at 7.¹¹ Rather, he simply concludes that a specimen

¹¹ To ascertain how a specimen was oriented *in vivo*, a pathologist must (i) identify anatomical landmarks, and (ii) consult markers provided by the explanting surgeon. Ex. DD, Westra, at 4; Ex.EE, Lester, at 7. Specifically, the surgeon must use sutures, tags, or a diagram to designate the orientation (*i.e.*, anterior, posterior, medial, lateral, superior, and inferior positioning) of the specimen. *See* Ex. DD, Westra, at 4; Ex. EE, Lester, at 7. The failure to adhere to this methodology at the time of explantation eliminates the pathologist’s ability to determine the *in vivo* orientation of the specimen, and renders conclusions as to its *in vivo* appearance speculative. *See* Ex. DD, Westra, at 4; Ex. EE, Lester, at 7.

that has a folded appearance during his examination was also folded *in vivo*. But as Dr. Maria Abadi—one of Ethicon’s expert pathologists—explained, “if [a mesh] comes [out] folded, it has nothing to do with the way it was positioned *in vivo*,” because the explanting surgeon subjects the explant to a variety of forces during the removal. *See* Ex. FF, Abadi 3/31/16 Dep. 99:19-101:9 (without information from the surgeon, orientation of specimens is “all speculation”).

Furthermore, Dr. Iakovlev admitted at deposition that he is unable to determine whether any alleged deformation occurs during the implantation procedure or *in vivo*. *See, e.g.*, Ex. G, Iakovlev 9/11/15 Dep. 213:12-24; 215:5-13; 216:20-24.¹² Dr. Iakovlev’s opinions regarding mesh curling or deformation are nothing but speculation, and should be excluded.

Finally, Dr. Iakovlev’s compartment theory is unsupported by data or literature, and simply makes no sense because the nerves, vessels, and tissue growing through the pore space cannot seal the pore in the manner Dr. Iakovlev suggests. *See* Ex. Q, Felix Report at 18. Crucially, Dr. Iakovlev does not identify any mechanism, nerve receptor, or substance derived from inflammation to explain how these alleged compartments could cause pain. *See* Ex. V, Vogel Report at 14. Dr. Iakovlev’s compartment theory is precisely the sort of novel theory that courts should exclude absent valid scientific support. *Rosen*, 78 F.3d at 319 (“the courtroom is not the place for scientific guesswork”).

For these reasons, the Court excluded Dr. Iakovlev’s folding and deformation opinions in Wave 1, noting that Plaintiffs did not bother to dispute the lack of reliability of these opinions. Wave 1 Iakovlev Order, at 8. The Court’s ruling on this Motion should be no different.

¹² Dr. Iakovlev also failed to consider that the highly elastic vaginal tissue into which Ethicon mesh products is implanted contracts immediately upon excision. *See* Ex. Q, Felix Report at 24 (explaining that the fixation of the specimen in formalin will exacerbate any deformation).

VII. Dr. Iakovlev Should Not Be Permitted to Offer Opinions Based On Mesh Not At Issue In This Case Or Mesh That He Cannot Identify.

Dr. Iakovlev seeks to explain his opinions using photographs of slides of mesh explants, many of which he has recycled from prior cases. *See* Ex. D, Iakovlev Report at 21-112. Yet, Dr. Iakovlev previously testified that he could not determine the origins of many of his slides. Ex. G, Iakovlev 9/11/15 Dep. 107:15-109:5; *see also id.* at 20:22-21:22 (explaining that he may have received slides from Dr. Kreutzer, who had received them from plaintiffs' counsel in pelvic mesh litigation). Dr. Iakovlev's opinions based on meshes not at issue in this litigation constitute the same sort of unreliable and irrelevant testimony that has been repeatedly excluded by this Court. *See* Wave 1 Iakovlev Order at 11-12.¹³

CONCLUSION

For the foregoing reasons, Ethicon requests that the Court exclude the opinion testimony of Dr. Iakovlev, and issue an order for a hearing pursuant to Federal Rule of Evidence 104, and such other and further relief as the Court deems proper under the circumstances.

Respectfully submitted,

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¹³ Plaintiffs in *Bellew* conceded that they would not question Dr. Iakovlev about the "about the other 130 surgical mesh explants he has analyzed prior to this case." Mem. Op. and Order, at 27, *Bellew v. Ethicon, Inc.*, No. 2:13-cv-22473 [Doc. # 265] (S.D. W. Va. Nov. 20, 2014).

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**IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
AT CHARLESTON**

IN RE ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	Master File No. 2:12-MD-02327 MDL 2327
THIS DOCUMENT RELATES TO: WAVE 4 CASES	JOSEPH R. GOODWIN U.S. DISTRICT JUDGE

CERTIFICATE OF SERVICE

I hereby certify that on April 13, 2017, I electronically filed the foregoing document with the Clerk of the Court using the CM/ECF system which will send notification of such filing to CM/ECF participants registered to receive service in this MDL.

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